REMARKS

In reply to the Office Action of December 11, 2008, applicant has amended claims 34, 41, 42, 47, and 48 to correct minor typographical errors. No claims have been added or canceled in this reply. Claims 1 to 34 are currently withdrawn. Accordingly, claims 34-48 are pending, with claims 34 and 42 in independent form. The amendments introduce no new subject matter.

35 U.S.C. § 103(a)

Claims 34-48 have been rejected as being allegedly unpatentable over Fantini, S. et al., "Assessment of the size, position, and optical properties of breast tumors *in vivo* by noninvasive optical methods," Applied Optics 37(10): 1982-1989 (1998) ("Fantini")[1] in view of Zeylikovich et al. (U.S. Patent No. 7,006,676, "Zeylikovich"). The Office alleges that Fantini discloses most of the limitations of claims 34 and 42, but admits that "Fantini is silent with respect to classifying a tumor as malignant or benign" (Office Action at page 7). The Office also alleges that this missing disclosure is present in Zeylikovich (see Office Action at pages 7-8). Applicants respectfully disagree that Fantini and Zeylikovich, alone or in combination, disclose the subject matter of the pending claims, for at least the following reasons.

Independent claim 34 covers a method of determining whether a tumor in a tissue sample is malignant or benign. The methods include "selecting two wavelengths of light to minimize a difference between relative changes in intensity of light transmitted through the tumor for the two wavelengths, wherein the relative changes in intensity of the light for each wavelength are measured relative to a background intensity of light transmitted through the sample." The Office purports to find this subject matter in Fantini at page 1983, paragraphs 1-3, and in Figure 1 (Office Action at page 6). Applicant respectfully disagrees, because in fact, this step is not disclosed in the cited portion or any other portion of Fantini.

Applicant's specification discloses methods in which two wavelengths of light are selected to minimize a difference between relative changes in light intensity following

[1] This reference is co-authored by the inventor of the present application.

transmission through a tumor. For example, the specification states that "[t]wo projections of each breast are typically acquired, craniocaudal and oblique, by illuminating the breasts with multiple wavelengths, preferably with at least some of the wavelengths in the range of 680 to 880 nm" (Specification at page 21, lines 14-16). Then, "[t]o perform the quantitative assessment, a pair of wavelengths is selected to minimize the intensity change induced by the region of interest ... [u]sing these two wavelengths, Eq. (7) is applied to compute the absolute oxygenation level within the region of interest" (Specification at page 21, lines 24-28). In one example, the change in intensity was measured at nine different wavelengths (680 nm, 720 nm, 730 nm, 758 nm, 768 nm, 776 nm, 800 nm, 840 nm, and 880 nm) and two wavelengths among the nine were selected for determination of the oxygenation level in the sample (see, e.g., Specification at page 27, line 23, through page 29, line 9).

Selection of two wavelengths to minimize a difference between relative changes in intensity of light transmitted through the tumor provides important advantages in the method disclosed in the present application. The specification states that "by appropriately choosing the two wavelengths λ_1 and λ_2, one can translate a measurement of the background scattering ratio into a measurement of the absorption-perturbation ratio associated with the embedded inclusion" (Specification, page 16, lines 17-20). The oxygen saturation of the inclusion can readily be determined based on measurements at the chosen wavelengths (see, e.g., Specification, page 18, Equ. (7)). Thus, the claimed method is believed to be "more robust in practical clinical measurements with respect to full reconstruction schemes" (Specification, page 19, lines 5-6). Applicant's experiments have shown that the "improved fit obtained to the actual oxygenation levels using the new methods is evident ... [n]one of the lines obtained using prior art perturbation analysis for a pair of wavelengths achieved a comparable fit to lines obtained using the new methods with a selected pair of wavelengths ... [t]hese results show that the new methods provided accurate measurements ... over the full range of oxygenation values and independent of the size and location of the [test object]" (Specification, page 28, lines 25-31).

Further, applicant's methods can be adapted to each investigation. That is, the pair of wavelengths can be selected for each particular tissue of interest; because different types of

tissue interact with light in different ways, the flexibility of the method ensures that improved accuracy in the determination of oxygenation can be realized for a wide variety of samples. Thus, the claimed method, in addition to being useful for investigating breast tissue, can be "applied to a wide variety of samples, including human brain, breast, and muscle tissue, as well as any organ that is optically accessible" (Specification at page 2, lines 10-11). The method can be used to "assess brain activity by measuring absolute levels of oxygenation, or to ... identify ischemic or underperfused [muscle] tissue regions" (Specification at page 32, lines 18-19).

In contrast, Fantini does not disclose the step of "***selecting*** two wavelengths of light ***to minimize a difference between relative changes in intensity of light transmitted through the tumor for the two wavelengths***, wherein the relative changes in intensity of the light for each wavelength are measured relative to a background intensity of light transmitted through the sample," as claim 34 requires. Instead, Fantini states that the "light sources are two laser diodes emitting at 690 and 825 nm, respectively" (Fantini, page 1983, col. 1). That is, Fantini merely uses two different light sources in his mammography instrument; he states that "our current prototype for frequency-domain optical mammography collects data at only two wavelengths" (Fantini, page 1988, col. 1). Thus, Fantini does not disclose the ***selection*** of two wavelengths *to minimize a difference between relative changes in intensity of transmitted light.*

Zeylikovich does not cure Fantini's deficiencies with regard to claim 34. There is no disclosure or suggestion in Zeylikovich to select two wavelengths of light to minimize a difference between relative changes in intensity of light transmitted through a tumor for the two selected wavelengths. Instead, like Fantini, Zeylikovich merely discloses that "the detection apparatus includes at least one and, more preferably, a pair of light sources" (Zeylikovich, col. 9, lines 25-27). As an example, Zeylikovich states that "one light source may emit ... most preferably, about 680 nanometers, while the other light source may emit ... more preferably, about 830 nanometers" (Zeylikovich, col. 9, lines 29-34). But Zeylikovich certainly does not disclose, or even suggest, selecting two wavelengths to minimize a difference between relative changes in transmitted light through a tumor.

Therefore, neither Fantini nor Zeylikovich, alone or in combination, discloses the subject matter of claim 34. Further, the method of claim 34 would not have been obvious to a person of ordinary skill in the art, because neither Fantini nor Zeylikovich discloses or even suggests selecting two wavelengths of light to minimize a difference between relative changes in intensity of light transmitted through the tumor for the two wavelengths. Further, applicant has been unable to find any disclosure in either Fantini or Zeylikovich that recognizes any advantage of taking such an approach. Thus, even if Fantini and Zeylikovich were combined as the Office suggests (which applicant does not concede is proper), the combination still would not teach all of the elements of claim 34.

Accordingly, applicant submits that independent claim 34 is patentable over Fantini and Zeylikovich, and respectfully requests reconsideration and withdrawal of the rejection of claim 34 under 35 U.S.C. § 103(a).

Next, independent claim 42 covers a method of determining whether a tumor in a tissue sample is malignant or benign. The method of claim 42 includes "calculating spatial second derivatives of products of the sample thickness and the intensities of the transmitted light at the locations for the two wavelengths of light." The Office purports to find this subject matter in Fantini at page 1984, and in Figures 2 and 3 (Office Action at page 6). Applicant respectfully disagrees, because this step is simply not disclosed in the cited portion or any other portion of Fantini.

Applicant's specification discloses that edge-corrected amplitude and phase images of samples are used "to create images based on an N-parameter, defined as $N(x,y) = r_0 ac_0 / r(x,y) ac(x,y)$, where r_0 is the maximum thickness of the sample, ac_0 is the AC amplitude at a pixel where the breast thickness is r_0, ac(x,y) is the amplitude measured at pixel (x,y), and r(x,y) is the breast thickness at that pixel derived from the phase information" (Specification at page 13, lines 5-9). The specification states further that images are "obtained by taking the second derivative (N′′)" (Specification, page 13, line 13). Methods for calculating spatial second derivatives of N are provided (see, e.g., Specification, page 13, lines 17-23).

Second derivative images have "enhanced contrast and identif[y] those areas in the image characterized by a local maximum" (Specification, page 14, lines 6-7).

In contrast, Fantini does not disclose calculating spatial second derivatives of products of the sample thickness and the intensities of the transmitted light at the locations for the two wavelengths of light. Page 1984 and Figures 2-3 of Fantini, which are cited by the Office, discuss determination of various parameters of the sample by ***fitting*** a photon diffusion equation to raw data that has been corrected for edge effects by using measured phase information. For example, Fantini states that "we reduced the edge effects by using the phase information to determine the breast thickness at each image pixel" (Fantini, page 1984, col. 1). Figure 2 shows "edge-effect-corrected optical mammograms" (Fantini, page 1984, col. 1). Figures 3(a) and 3(b) show measured and fitted data for the ac amplitude and phase, respectively, of a portion of the corrected mammogram (see, e.g., Fantini, page 1984, col. 2).

However, Figures 2 and 3 do not relate in any way to spatial second derivatives. Moreover, no other portions of Fantini disclose or relate to spatial second derivatives of any of his measured data. Instead, Fantini states that he "exploit[s] the phase information, in addition to the intensity information, to determine the size, depth, and optical properties of the tumor" (Fantini, page 1984, col. 1) by fitting normalized ac and phase information "to the diffusion problem of light transmission through an infinite slab-shaped turbid medium that contains a spherical inhomogeneity" (Fantini, page 1985, col. 2). The parameters that Fantini derives, summarized in Table 3, are ***fitting parameters*** that are determined in his fitting procedure; they are not determined by calculating spatial second derivatives.

Zeylikovich does not cure Fantini's deficiencies with regard to claim 42. Applicant has not been able to find any disclosure or suggestion in Zeylikovich to calculate spatial second derivatives of products of the sample thickness and the intensities of the transmitted light at the locations for the two wavelengths of light, as claim 42 recites. Instead, Zeylikovich discloses measuring the amplitude and phase of light transmitted through a sample, and then numerically "solv[ing] the diffusion equation for the unknown parameters at each wavelength" (Zeylikovich, col. 15, lines 38-39). Zeylikovich does not disclose calculating spatial second derivatives in his

methods. Applicant's search of Zeylikovich revealed that the words "spatial" and "derivative" do not even appear in his disclosure, and applicant has been unable to find any other disclosure in Zeylikovich that relates to spatial derivatives, but may be presented in alternative terms.

Independent claim 42 also recites the steps of "calculating an oxygenation level of the tumor based on the spatial second derivatives" and "calculating an oxygenation level of non-tumor regions of the tissue sample based on the spatial second derivatives." As explained above, applicant has been unable to find any disclosure in either Fantini nor Zeylikovich relating to spatial second derivatives. Not surprisingly, applicant has been similarly unable to find any disclosure in either reference relating to the calculation of an oxygenation level in a tumor or in non-tumor regions based on spatial second derivatives. In view of the failure of either reference to disclose or suggest calculating spatial second derivatives, both references also fail to disclose or suggest the further calculation steps based on spatial second derivatives recited by claim 42.

Thus, for all of the foregoing reasons, neither Fantini nor Zeylikovich, alone or in combination, discloses the subject matter of claim 42. Further, the method of claim 42 would not have been obvious to a person of ordinary skill in the art. Neither Fantini nor Zeylikovich discloses or suggests calculating spatial second derivatives of products of the sample thickness and the intensities of the transmitted light at the locations for the two wavelengths of light. Further, applicant has been unable to find any disclosure in either Fantini or Zeylikovich that recognizes any advantage of taking such an approach. Thus, even if Fantini and Zeylikovich were combined as the Office suggests (which applicant does not concede is proper), the combination still would not teach all of the limitations of claim 42.

Accordingly, applicant submits that independent claim 42 is patentable over Fantini and Zeylikovich, and respectfully requests reconsideration and withdrawal of the rejection of claim 42 under 35 U.S.C. § 103(a).

Each of claims 35-41 and 43-48 depends from either claim 34 or claim 42, and is therefore patentable over Fantini and Zeylikovich for at least the same reasons as claims 34 and

42. Therefore, applicant respectfully requests reconsideration and withdrawal of the rejections of each of claims 35-41 and 43-48 under 35 U.S.C. § 103(a).

CONCLUSION

Applicant submits that all pending claims are now allowable and respectfully requests a notice of allowance. It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify agreement with or concession of that rejection, issue, or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper.

No fees are believed to be due. Please apply any charges or credits to Deposit Account 06-1050, referencing Attorney Docket No. 10851-0008US1.

Respectfully submitted,

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J. Peter Fasse
J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

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